DEVELOPMENT AND EVALUATION PARAMETERS OF SUSTAINED RELEASE TABLET

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Abstract: Formulating sustained release tablets is typically accomplished through one of three methods: wet granulation, direct compression, or the dispersion of solid particles inside solid particles within a porous matrix made from a variety of polymers such as poly methyl methacrylate (PMMA), polyglycolic acid, or high-performance microcrystalline cellulose (HPMC). The rate at which the medication is released is controlled by the matrix. Release retardants, such as HPMC, are an essential component of the formulation's excipient because of their capacity to assist in continuous release. Compressing the mixture of the drug, the retardant material, and the additives is one way to make a tablet in which the medication is encapsulated inside a matrix core of the retardant. Granulating the mixture beforehand is another option that may be used before compression. Matrices that are mineral or biodegradable, as well as those that are fond of water or oil, may be used in this process. Experiments of dissolving in vitro are helpful for establishing the pace at which drug is released into the body. Since sustained release tablets may ensure greater patient compliance by reducing both the total dosage and the dosing schedule, they may be highly effective in the treatment of chronic illnesses. This is because the total dose and the dosing schedule can be reduced.

Keyword: Sustained release, Polymer, Formulation, Evaluation parameters.

INTRODUCTION:

Innovative drug delivery systems that provide sustained, controlled dispersion and/or site-specific targeting may be able to improve the therapeutic effectiveness of integrated medicines. In order to be successful, a drug delivery system must first and foremost be able to swiftly achieve and then maintain the therapeutic concentration of the medicine at the site of administration inside the body. Oral sustained release delivery systems are designed with a number of different factors in mind, including the medical condition being treated, the patient, the length of therapy, and the characteristics of the drug itself [1]. A "sustain release system" refers to any kind of medication delivery system that allows for the controlled and measured distribution of an active ingredient over a prolonged period of time. As a result of its enormous dose capacity, simple production process, and ability to make use of already established infrastructure, matrix tablets are often considered to be the most economically feasible

sustained action dosage form [2]. Innovative formulations that allow extended drug release using matrix-based formulation utilising conveniently available, low-cost excipients continue to draw the interest of researchers in the field of study. In the last twenty years, there has been a significant increase in the amount of research and development that has gone into the creation of medicine delivery systems that provide continuous release [3]. This is as a result of a number of factors, including the high price tag associated with developing new drug entities, the ageing of the global patient population, the discovery of new polymeric materials that are well-suited to extending the drug release, and the enhancement of therapeutic efficiency and safety brought about by these delivery systems. Specifically, the ageing of the global patient population. Technology that allows for prolonged release is being used more often in animal health products [4].

ADVANTAGES

i) Patient compliance:

Noncompliance with medication treatment is most often encountered in the setting of chronic conditions that need ongoing medical attention. This is because the success of drug therapy is dependent on the patient's ability to comply with medication treatment [5]. A patient's willingness to comply with a treatment plan may be increased by increasing knowledge of the disease process, the patient's confidence in the treatment, and the patient's awareness of the treatment plan's demands. Not to mention the negative consequences that the dosage form may have on the body as a whole, as well as the high cost of therapy and the difficulty of developing effective therapeutic regimens. A possible answer to this problem may be found in the form of pharmaceutical delivery systems that use sustained release [6].

ii) Reduced 'see-saw' fluctuation:

When a drug is taken in the form of its typical dosage, the concentration of the medicine in the blood and in other tissues of the body often exhibits a "see-saw" pattern. Pharmacokinetic parameters, such as the drug's absorption, distribution, excretion, and the amount of time that passes between doses, have a significant amount of control over these fluctuations. The'see-saw' pattern is particularly obvious in the case of drugs that have a biological half-life of less than four hours [7]. This is because recommended dosage intervals are seldom fewer than four hours. A sustained-release drug delivery system has the potential to drastically reduce the number of times a medication needs to be administered by allowing the user to control the rate at which the medication is released into the bloodstream of the body and into the cells of the organ or tissue that is its intended target [8].

iii) Total dose reduction:

The total amount of medicine that must be taken to treat an illness may be cut down using delivery systems that allow for sustained drug release. By reducing the dosage of the medicine, it may be possible to lessen the severity of side effects, whether they occur systemically or locally. Additionally, this would be beneficial to the economy [9].

iv) Improvement of deficiency in treatment:

It is essential to the successful treatment of a disease that active drugs be delivered to the tissues and organs that need treatment. Most of the time, in order to achieve a therapeutically effective concentration, a dose that is far greater than what is required in the cells has to be administered. It is undesirable if this were to happen since it might have toxicological and immunological effects on tissue that is not the intended target. Using a dosage type that has a longer release makes it feasible to have better control over an acute or chronic sickness [10].

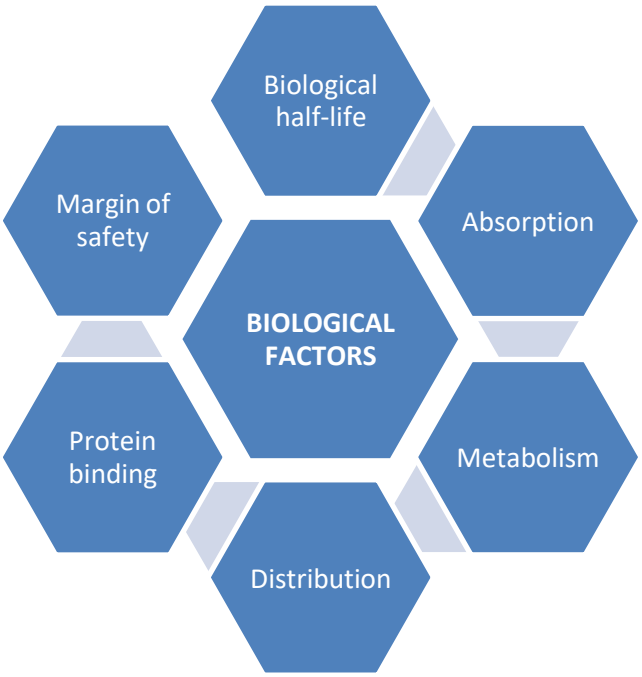
v) Economy:

It is common for the unit cost of sustained release pharmaceuticals to be greater than that of regular dose forms; however, the average cost of treatment over an extended period of time may be lower when using these medications because of the distinctive qualities of these substances [11].

DISADVANTAGES OF SUSTAINED RELEASE DOSAGE FORM:

1. Incorrect formulation may result in the dumping of the dose.
2. A decreased ability to modify the dosage as needed.
3. The price is higher than that of traditional dosage forms.
4. Raise the possibility of first-pass metabolism.
5. Patient education is important in order to take medicine correctly.
6. There is a possibility of a decrease in the overall availability.
7. Poor correlations between in vivo and in vitro experiments [12].

BIOLOGICAL FACTORS INFLUENCING RELEASE FROM MATRIX TABLET:



1) Biological half-life:

The primary goal of an oral sustained-release (SR) formulation is to maintain therapeutic blood levels for the longest period of time feasible. This is something that can only be achieved if the drug is absorbed into the circulation at a pace that is almost equivalent to the rate at which it is eliminated from the body. The rate at which a drug is eliminated from the body is referred to as its elimination rate, and it differs from one substance to another. The processes of elimination include metabolism, the excretion of urine, and everything else that is necessary to remove the drug from the body permanently [13].

For pharmaceuticals with short half lives, the sustained-release formulation is the way to go. Such medications like levodopa, which have a half life of less than two hours, are not good candidates for extended release formulation. It is not recommended to use the SR formulation for long-acting medicines that have a half-life of more than eight hours. Two examples of medications that fall within this category are digoxin and phenytoin [14].

2) Absorption:

In order to do this, the rate of release of an SR product has to be much slower than the rate of absorption. In light of the fact that the majority of pharmaceuticals need between 8 and 12 hours to go through the absorption zones of the GI tract, the maximum potential half-life for absorption should be somewhere between 3 and 4 hours. If this does not happen, the dose form will have already left the probable absorption zones before the medication release is finished [15]. This results in an apparent absorption rate constant of 0.17–0.23h-1, which corresponds to an overall efficiency of 90–95 percent across the whole of this time period. Because of this, it

recognises the small intestine as a location in the body where drug absorption occurs more or less regularly. It is conceivable that the SR preparation will impede the absorption of a medication whose absorption is dependent on active transport or which can only take place in a certain region of the stomach [16].

3) Metabolism:

It has been established that taking a medication in a form that allows for a slower release decreases bioavailability. When given in a slow-release dosage form, medications that are subject to considerable first-pass metabolism in the intestinal lumen or tissue may have a lower bioavailability. Formulations with a sustained release are a possibility for medications that have a poor water solubility. After the formulation for the Sustain Release method has been created, it is possible to increase the medication's solubility in order to accomplish this objective. Even though the crystallisation of medicine before it enters systemic circulation is very improbable,it is nevertheless crucial to take the necessary steps to prevent it at this period [17].

4) Distribution:

The apparent volume of distribution that a medication has throughout the body has a considerable influence on the rate at which it is removed from the body. These medications are not suitable choices for the oral SR drug delivery technique because the elimination rate is altered by the drug's apparent volume of distribution. Examples of such substances include the drug chloroquine [18].

5) Protein Binding:

Due to the fact that all medications are bound to plasma and/or tissue proteins, the concentration of the drug that is not protein-bound is more important for pharmacological response than the concentration of the drug that is protein-bound. Since significant binding to plasma increases the biological half-life regardless of dose form, SR drug delivery systems are sometimes unnecessary for drugs whose therapeutic effects are mostly determined by protein binding. This is because substantial binding to plasma increases the biological half-life [19].

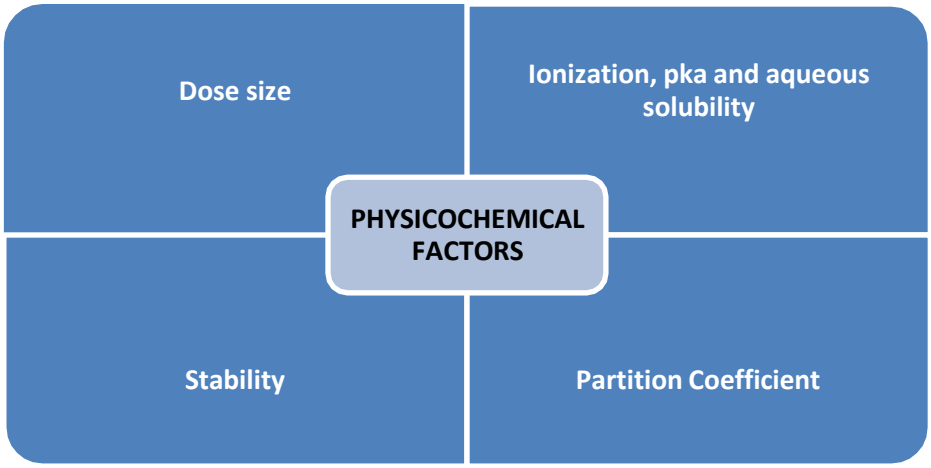
6) Molecular size and diffusivity:

A number of distinct kinds of sustained release systems call for drug diffusion to take place across a membrane or matrix that controls the rate of diffusion. The molecular size of a drug and its capacity to traverse membranes are two factors that influence the drug's diffusivity, also known as its diffusion coefficient. One of the most important factors that goes into calculating the actual diffusion coefficient. In polymers, the letter 'D' is used to signify the molecular size, also known as the molecular weight, of the species that is diffusing [20].

7) Margin of safety:

If a medication has a therapeutic index that is greater, then there is generally less of a chance that it may have adverse effects in patients. When it comes to low-therapeutic-index medications, oral SR drug delivery methods are not the best option [21].

PHYSICOCHEMICAL FACTORS INFLUENCING RELEASE FROM MATRIX TABLET:



a) Dose size:

The maximum safe dosage for a single administration of most medications is anywhere between 500 milligrammes and one gramme. In addition, these conditions must be satisfied by the sustained-release pill form. Substances are considered to have a big dosage size if they either need a large number of doses or are transformed into liquid systems. Another thing to take into consideration is the margin of safety, which involves administering a significant quantity of a drug that has a limited therapeutic range [22].

b) Ionization, pka and aqueous solubility:

Most often, drugs may be thought of as extremely weak acids or bases. Even if medications in their original form may be able to pass across lipid membranes, the environment in which the chemical is absorbed has a substantial impact on the pka of the molecule. The medication's chances of being absorbed are increased when it is delivered in the form in which it was first created. Unfortunately, the water solubility decreases as the process of converting to an unmodified form becomes more complex [23]. The solubility of the medicine in water is an important consideration for both the diffusion and the dissolution-based delivery methods. The stomach is an acidic environment, while the small intestine has a more neutral pH, therefore itis necessary to analyse the impact that Phone has on the release mechanism for each of these dosage types. Low soluble compounds (0.01 mg/ml) are naturally maintained because the rate of dissolution of a drug in a dosage form restricts the rate at which it is released over the time period of delivery in the gastrointestinal system. Because the concentration of the medication

in solution acts as the driving force for diffusion, it stands to reason that substances with restricted solubility would not make good candidates for drug treatment [24].

c) Partition Coefficient:

When a drug is ingested into the body via the digestive tract, it must first cross a number of biological membranes before it can have an effect anywhere else in the body. It is a common assumption that membranes are lipidic, therefore determining the partition coefficient of oil-soluble medications is essential to determining the efficiency of membrane barrier penetration [25]. The partition coefficient of oil-soluble medicines is critical. Compounds that are lipophilic and have a high partition coefficient tend to have a low solubility in water and may be found accumulating in fat cells. When a chemical is unable to pass through a membrane, as is the case with compounds that have a low partition coefficient, the result is poor bioavailability. This is because the membrane prevents the passage of the compound. Partitioning effects may also be seen in the process of diffusion via polymer membranes. When choosing a membrane with a diffusion-limiting property, it is important to take into consideration the drug's partitioning characteristics [26].

d) Stability:

drugs that, after being taken orally, are metabolised by the action of acid-base hydrolysis and enzymes. As a result of the fact that a drug in solid form would still degrade, although at a more leisurely rate, this formulation of delivery is one that is very desired under difficult circumstances. For dosage forms that are prone to instability in the stomach, delivery methods that can be extended throughout the whole of the digestive tract's journey are of great assistance [27]. The same constraints apply to delivery methods that delay drug release until the dosage form reaches the small intestine. The bioavailability of substances that are broken down in the small intestine might be decreased by using a dosage form that provides continuous release. This is due to the fact that the small intestine is the location of enhanced pharmaceutical delivery as well as increased medication breakdown [28].

FORMULATION

A) Diffusion sustained system:

The concentration of drug molecules gradually decreases as they go from an area of high concentration to an area of low concentration. The rate of diffusion of a certain substance J over a membrane is described by Fick's law as a function of the substance's concentration [29].

$J = - D \, dc/dx$

D = diffusion coefficient in area/ time dc/dx = change of concentration 'c' with distance ‘x’ In common form, when a water insoluble membrane surrounds a core of drug, it must diffuse through the membrane, the drug release rate dm/dt is given by,

$$dm/dt = ADK.\ C/L$$

Where, A = Area

K = Partition coefficient of drug between the membrane and drug core.L= Diffusion path length (i.e. thickness of the coat in ideal case).
C = Concentration difference across the membrane.

i) Diffusion reservoir system:

In this case, the medication is shielded by a polymeric covering that is water-resistant and non-soluble. The medication that is contained inside the tablet or particle will partition into the membrane and then be exchanged for fluid from the environment around it. The drug will eventually make its way to the outside of the polymer and will interact with the surrounding environment as more of it is added. The mechanism that is responsible for the release of the drug is called diffusion [30].

ii) Diffusion Matrix type:

When a drug in the form of a solid is placed into a matrix that is insoluble, the rate at which the drug is released from the matrix is contingent upon both the drug's ability to diffuse and the solubility of the solid. Higuchi has successfully determined the appropriate drug release equation for this apparatus by calculation [31].

$$Q = D/T\ [2A–Cs]\ Cst\ ½$$

Where, Q = weight in gms of drug released per unit area of surface at time t.D = Diffusion coefficient of drug in the release medium.
ε= porosity of the matrix.

Cs = solubility of drug in release medium.T = Tortuosity of the matrix.

A = concentration of drug in the tablet, gm/ ml.

The release rate can be given by following equation:-

$$\text{Release rate} = AD/ L = [C1-C2]$$

Where, A = Area
D = Diffusion coefficient

C1 = Drug concentration in the core

C2 = Drug concentration in the surrounding mediumL = Diffusion path length

B) Dissolution sustained systems:

Medication that dissolves slowly is more likely to remain unchanged within the body, however the dissolution rates of medicines with a high water solubility may be slowed down by producing the right salt or derivative. These methods are often used in the production of enteric-coated dosage forms. Protecting the stomach against drugs such as aspirin requires the application of a coating that degrades when exposed to natural or alkaline environments. The release of the medication from the dosage form is delayed until it reaches the more acidic environment of the stomach [32].

a) Soluble reservoir system:

An erodible layer is placed on top of the medicine as well as the layers of the rate-controlling coat that are used in this method. Both of these layers are sandwiched between layers of the drug [33].

b) Soluble matrix system:

It is possible that it is a sphere or pill that has been impregnated with medication, and the process of erosion will be extremely slow [34].

C) Methods using Ion Exchange:

Ion exchange resin is an intriguing method for sustained drug delivery since the drug release characteristic is less impacted by environmental factors such as enzyme concentrations and pH at the absorption site zero order release. Utilizing this strategy to do kinetic efficiently is a possibility [35].

It's possible that an ion-exchange based delivery technique is the best option for you if your drug can be quickly metabolised by enzymes. Ion exchange resin comes in a number of different varieties [36].

- Cation exchange resin:
- Anion exchange resin:

Cationic exchange resin:

possessing an acidic functional group as one among its constituents. The majority of situations include the presence of a polysteryne phenolic carboxylic phenolic group [37].

Anion exchange resin:

included the participation of a fundamental functional group that was able to easily remove acidic anions. It is based on the idea that negatively or positively charged drug moiety would combine with appropriate resin to generate insoluble poly salts, and this is how ion exchange resin are used to extend the effect of the medication [38].

4) pH– Independent formulations:

The length of the delay may be reduced in duration by eliminating some components of the oral route of administration; nevertheless, the chemical environment that exists throughout the whole of the gastrointestinal system is a challenge for the formulation of dosage forms. Because the vast majority of drugs may be classified as either weak acids or bases, the pH of their sustained release formulations is a very important aspect to consider. It is common practise to include buffers in a formulation [39]. These can take the form of salts of amino acids, citric acid, phthalic acid, phosphoric acid, or tartaric acid. Their purpose is to assist in maintaining a stable pH, which in turn allows the medicine to be released regardless of the pH of the body. The standard procedure for the preparation of buffered sustained release formulation involves combining an acidic or basic medication with one or more buffering agents, granulating the mixture with suitable pharmaceutical excipients, and coating it with a film-forming polymer that is permeable to gastro-intestinal fluid. When stomach acid penetrates the capsule membrane, the buffering agents change the pH of the fluid contained inside the capsule in order to ensure a constant release rate of the drug [40].

5) Altered density formulations:

If not all of a dosage form's components are absorbed by the body via the digestive system, that dose form will have a reduced level of efficacy. In order to accomplish this objective, a number of approaches have been developed to lengthen the amount of time a drug is in contact with the digestive system [41].

High density approach:

The pellets that are utilised in this procedure should have a density that ranges from one to four grammes per cubic centimetre, which will make them heavier than the average contents of the stomach. In this kind of formulation, the medication is either covered with a heavy core or combined with heavy inert substances such as barium sulphate, titanium dioxide, iron powder, and zinc oxide [42].

Low density approach:

Polystyrene, pop rice, and popcorn are all used as carriers; the surface of the empty shell is

undercoated with sugar or a polymeric material such as methacrylic polymer and cellulose acetate phthalate, which enables the medication to be released gradually in the stomach. After the medication has been mixed with a polymer such as ethyl cellulose or hydroxypropyl cellulose, it is then applied to the undercoating of the capsule. Because of this, the ultimate product is a drug that has a gradual onset of action and remains suspended in the stomach for a considerable amount of time [43].

POLYMERS USED IN MATRIX TABLET:

Hydrogels:

Polyhydroxyethylemethylacrylate(PHEMA),Crosslinked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone(PVP),Polyethylene-oxide(PEO), Polyacrylamide (PA) [44]

Soluble polymers:

Polyethyleneglycol (PEG), Polyvinyl alcohol(PVA), Polyvinylpyrrolidone (PVP), Hydroxypropylmethylcellulose (HPMC) [44]

Biodegradable polymers:

Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters [44]

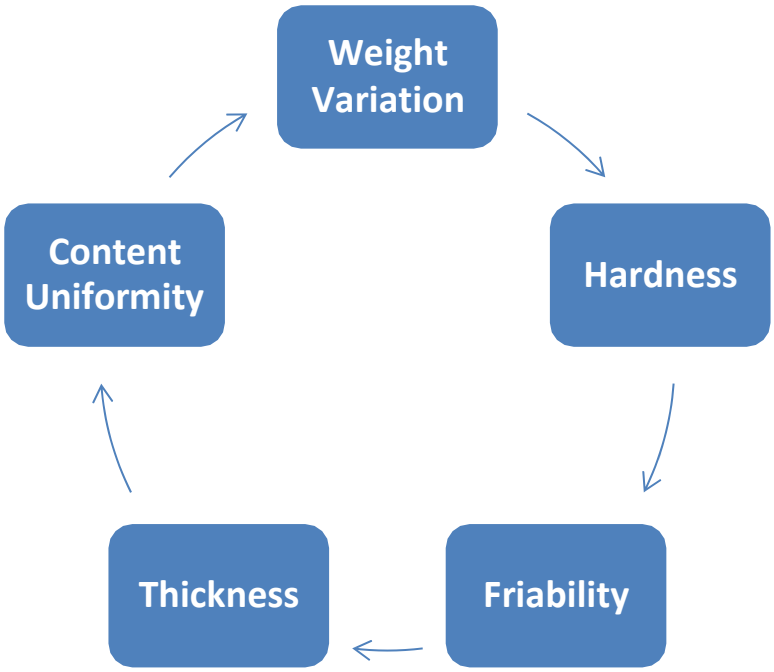
Non-biodegradable polymers:

Polyethylene vinyl acetate (PVA), Polydimethylsiloxane(PDS), Polyetherurethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC) [44]

Mucoadhesive polymers:

Methyl cellulose, polyacrylic acid, tragacanth, sodium carboxy methyl cellulose, polycarbophil, and sodium carboxy methyl cellulose locust bean gum, karaya gum, xanthan gum, and guar gum. Polycarbophil and sodium carboxy methyl cellulose [45].

EVALUATION TEST FOR SUSTAINED RELEASE TABLETS:



Weight Variation:

To arrive at the value that represents the average weight of 20 tablets, we first weighed each pill individually, and then added together the findings [46].

Hardness:

The hardness of tablets from each batch was measured using a Monsanto tester, and the average values were calculated from those readings [47].

Friability:

The friability of the tablets was determined by utilising a Roche friabilator that rotated at 25 revolutions per minute for four minutes [48].

Thickness:

For the purpose of measuring tablet thicknesses, a micrometre screw gauge was used [49].

Content Uniformity:

A UV-visible spectrophotometer was used in conjunction with a calibration curve in order to ascertain the amount of drug present [50].

IN VITRO DISSOLUTION STUDY:

In research, the Rotating Paddles device is used rather often in order to assess drug release. The word "solvent" may also refer to buffer. The temperature of the bath is maintained at 370

degrees Celsius, and the dissolving medium that is used in the process of releasing the drug is sampled at regular intervals and refilled in the same volume. In order to determine how much of the medicine is being distributed, an ultraviolet (UV) spectrophotometer is used. The progression of the drug's breakdown over time is shown as a curve that shows the percentage release versus time [51].

Short Term Stability Study:

The examination into short-term stability was conducted with the intention of determining whether or not the release profile of the optimal batch altered while it was being stored [52].

CONCLUSION:

This review study has focused on the formulation, advantages, and drawbacks, as well as the various polymers that are used in the manufacturing of sustained-release matrix tablets. In light of what has been said so far, it is possible to draw the conclusion that matrix tablets are helpful for resolving concerns with patient compliance as well as the effectiveness of dosage form in eliciting the right therapeutic response. The benefits include an affordable price and a convenient location (just needing to be taken once day). Because of this, there has been a move toward improving the dosage form design of sustained-release matrix tablets in order to maximise their effectiveness.

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